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Autonomic nervous system regulation in chronic neck- shoulder pain

Relations to physical activity and perceived stress

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Abstract

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Neck-shoulder pain (NSP) is a highly prevalent musculoskeletal disorder with unclear causes, and effective prevention and treatment require a further understanding of the underlying mechanisms. Aberrant autonomic nervous system (ANS) regulation is a hypothesized causal element in the development and maintenance of chronic muscle pain.

The overall aim of this thesis was to investigate possible differences in ANS regulation between chronic NSP and healthy control (CON) groups using both laboratory assessment and ambulatory monitoring in daily life.

Four papers are included in this thesis, based on data from three groups with chronic NSP. Autonomic responses to laboratory stressors were assessed using heart rate variability (HRV), blood pressure, trapezius muscle activity and blood flow measurements (Study I) in NSP and CON. Long-term ambulatory monitoring of HRV, physical activity and perceived symptoms were assessed in Studies II and IV to investigate group differences in real-life conditions. Finally, the effects of a ten-week intervention (using individually adjusted HRV biofeedback) to reinstating ANS balance in subjects with chronic NSP were evaluated using self-reported symptoms and health ratings, as well as autonomic regulation testing (i.e., evaluating HRV at rest and in response to stress) (Study III).

The main findings from the four studies demonstrated aberrant ANS regulation in the NSP group compared to CON, which was predominantly characterized by diminished parasympathetic cardiac activity during rest and sleep, and altered sympathetic reactivity to laboratory stressors (Studies I, II and IV). Different patterns in physical activity were observed between the NSP and CON groups, with reduced physical activity during leisure time in the NSP group (Studies II and IV). Physical activity was found to be positively associated with HRV. Positive effects of HRV-biofeedback were found on perceived health, including social function, vitality and bodily pain, and improved HRV (Study III).

In conclusion, imbalanced ANS regulation was demonstrated among persons with chronic NSP at both the systemic and local levels. Diminished parasympathetic activity in NSP was modulated by lower levels of physical activity in leisure time. Interventions targeting ANS functions might benefit persons with chronic NSP.

Keywords: Autonomic imbalance, Daily physical activity, Trapezius myalgia, Treatment, Parasympathetic, Sympathetic

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Hallman DM, Lindberg L-G, Arnetz BB, Lyskov E. Effects of static contraction and cold stimulation on cardiovascular autonomic indices, trapezius blood flow and muscle activity in chronic neck-shoulder pain. *European Journal of Applied Physiology*, 2011, 111(8): 1725-1735.
- II Hallman DM, Lyskov E. Autonomic regulation, physical activity and perceived stress in subjects with musculoskeletal pain: 24-hour ambulatory monitoring. *International Journal of Psychophysiology*, 2012, 86(3): 276-282.
- III Hallman DM, Olsson E, von Shéele B, Melin L, Lyskov E. Effects of Heart Rate Variability Biofeedback in Subjects with Stress-related Chronic Neck Pain: A Pilot Study. *Applied Psychophysiology and Biofeedback*, 2011, 36: 71-80.
- IV Hallman DM, Hed Ekman A, Lyskov E. Physical activity and autonomic regulation in workers with chronic neck-shoulder pain – monitoring during work and leisure time (*Submitted manuscript*).

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Abbreviations

ANS	Autonomic Nervous System
CON	Control group
CPT	Cold Pressor Test
DBT	Deep Breathing Test
EMG	Electromyography
HF	High Frequency
HGT	Hand Grip Test
HRV	Heart Rate Variability
HPA	Hypothalamic Pituitary Adrenal
LF	Low Frequency
MET	Metabolic Equivalent
MSD	Musculoskeletal Disorder
NSP	Neck-Shoulder Pain group
PA	Physical Activity
PNN50	Proportion of RR interval differences >50ms
PNS	Parasympathetic Nervous System
RMSSD	Root Mean Squared Successive Differences
RRI	R-to-R Intervals
RSA	Respiratory Sinus Arrhythmia
SDNN	Standard Deviation of RR intervals
SNS	Sympathetic Nervous System
VLF	Very Low Frequency

Introduction

Musculoskeletal disorders (MSDs) constitute a major health problem both in the general population (1) and in workers (2), and typically include chronic pain and discomfort in muscles of the lower back, neck, shoulders or the upper extremities (arm, wrist, hand). Neck-shoulder pain (NSP) is one of the most common work-related MSDs to date, with an annual prevalence ranging between 30% and 50% (1, 2). NSP is frequently reported in a variety of occupations, particularly among sedentary jobs where the physical demands are low (3-6). Women are more frequently affected than men (7). Considering the costs due to sick leave and loss in productivity, in addition to the negative effects on different aspects of quality of life among the afflicted individuals, MSDs place a considerable burden on society (8-10).

The purpose of the current thesis was to investigate possible differences in autonomic nervous system (ANS) regulation between persons with chronic NSP and healthy controls, with a focus on the influence of daily physical activity and perceived stress on autonomic regulation.

Neck-shoulder pain

Diagnosis

NSP consists of various symptoms, including muscle pain, stiffness or tightness of muscles and tenderness at palpation (11), as accompanied by fatigue, disability and poor physical and mental health (10, 12). As adequate objective markers are lacking, diagnosis is generally based on self-reports, which makes the basis for the diagnostic criteria relatively vague (11, 13). Thus, disorders of the neck-shoulder region are often referred to as non-specific myalgias according to the *International Classification of Diseases* (ICD). In this thesis, NSP is defined as perceived pain primarily from the neck and the surrounding tissues (Fig. 1), also referred to as trapezius myalgia or tension neck syndrome (ICD-10, code M 79.1). Acute or recurrent NSP may develop into chronic pain, as defined by pain lasting more than six months. In this condition, pain is mainly believed to originate from the muscles, although other structures such as joints, tendons and ligaments as well as nerves may also be affected. Different clinical diagnoses, for instance neck myalgia,

cervicobrachial syndrome (ICD-10, M 53.1) and cervicalgia (ICD-10, M 52.2), share similar patterns of self-reported symptoms, although they may involve different pathophysiological mechanisms. The lack of a specific diagnosis makes recommendations for causal treatment more difficult.

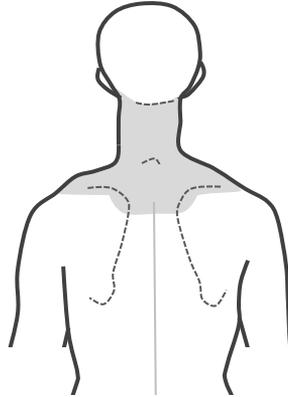


Figure 1. The figure illustrates the typical region of neck-shoulder pain in the current study.

Risk factors

Exposure risk factors for NSP consist of high biomechanical loads, monotonous repetitive movements, awkward postures, sedentary work, and psychosocial stress (2, 14-17), which induce unfavourable physiological responses in the body (11). In many cases, there is a higher risk of developing musculoskeletal pain when different exposures are combined (11, 18). An abundance of epidemiological studies indicate that stress-related factors at work are associated with NSP (18-20). For instance, high demands, low social support, low job control, and low influence were associated with neck pain (14), in accordance with the Job Demand-Control model (21). Another theoretical model, Effort-Reward-Imbalance (22), proposes that stress and negative emotions increase when there is an imbalance between efforts invested in work performance and the rewards received afterwards. Perceived stress seems to play an important role in both acute and chronic pain, and particularly in the transition from acute to chronic problems (15, 19). Studies have also shown that individual factors, such as female gender (7), older age (2) or genetics (23, 24) increase the susceptibility for the development of chronic NSP.

Mechanisms

A variety of different potential mechanisms are involved in the pathogenesis of NSP. Both local muscular processes and central mechanisms have been considered in the literature (11, 25-27). It has been proposed that sustained low-level muscle activity and reduced muscular rest, impaired muscle blood flow and altered motor control play causal roles in the development and/or maintenance of regional muscle pain (26). It is not likely, however, that a single physiological process could explain the occurrence of NSP, which rather seems to be of a multi-factorial origin. A variety of factors (e.g., external exposures and organizational, physiological, psychological, behavioural and individual factors) may interact differently depending on the progression of symptoms, e.g. acute, recurrent or chronic pain (28).

It is important to learn more about the dominating mechanisms involved in the pathogenesis. This may optimize mechanism-based interventions, and improve strategies for the prevention and treatment of chronic NSP.

Muscle pain and nociception

The *International Association for the Study of Pain* defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. This definition encompasses the multidimensional aspects of pain, as well as its complexity. The psychological dimension such as feelings of unpleasantness, fear and future beliefs, and the neural dimension (sensory/nociceptive) of pain are represented by various interacting structures in the brain, which together constitute a central network (29). Muscle pain is difficult to localize and may be perceived as “aching” and “cramping”, which distinguishes it from cutaneous pain (30). Pain signals originating from the musculoskeletal system are transmitted via small-diameter afferent fibres. The nociceptive nerves are constituted by slow conducting thin-myelinated (A- δ , Group III) fibres or non-myelinated (C, Group IV) fibres (31). The free nerve endings, i.e. nociceptors, are located in the wall of the arterioles and the surrounding connective tissue (30). The afferent nerves project to the dorsal horn of the spinal cord (lamina I and lamina V), and the signals are further transmitted via the brainstem to higher centres in the brain: the thalamus and the hypothalamus, and the insular, anterior cingulate and sensory cortices as well as the prefrontal cortex. In turn, afferent nociceptive signals are modulated by descending pain-inhibitory pathways (32). Muscle nociceptors are activated by tissue damage or mechanical stimuli, although they can also be sensitive to changes in the biochemical milieu, including the accumulation of metabolites and inflammatory substances as well as increasing levels of adrenaline (33, 34). Periph-

eral sensitization of nociceptors is accompanied by a decrease in mechanical threshold so that the receptor will respond to weaker mechanical stimuli. Persistent afferent signalling to the spinal cord may induce functional changes and re-organization (neuroplasticity). This may contribute to an amplified responsiveness of central neurons to incoming stimuli, i.e. central sensitization (31, 35). The transition from subacute muscle pain to chronic or widespread symptoms is related to sensitization at both the peripheral and central levels (25, 31, 36).

Stress responses and “allostatic load”

The human body needs to constantly adapt to challenges in the environment in order to maintain homeostasis. The term “stressor” describes a variety of different external or internal exposures that affect the body, while “allostasis” refers to the active process of achieving stability in adaptive systems through change (37, 38). The latter is mainly achieved through physiological activation in two key stress response systems: the ANS and the hypothalamic-pituitary-adrenal (HPA) axis, including various mediators (39). In daily life, we encounter an abundance of different stressors. These are normally harmless as the body is able to meet the demands by eliciting an acute stress response, which normally vanishes after the stressor has disappeared. A state of stress may occur when homeostasis is threatened or when the physiological response systems are strained and can no longer adequately adapt to the external or internal challenges (40). According to McEwen (37), “allostatic load” refers to an imbalance in the stress response systems that promote adaptation. There are mainly three types of physiological responses that can result in allostatic load: (i) the frequency and magnitude of the response could lead to allostatic load if stressful events are repeated frequently without adequate recovery between episodes; (ii) allostatic load may also occur due to an inability to shut down the stress response after the cessation of exposure, or when the stressor, such as muscle pain, persists over a long period of time; (iii) in a third scenario, the stress response is inadequate and the physiological systems may fail to respond to stressors, as in the case of fibromyalgia (41). Consequently, if one system is unable to respond sufficiently an increased load will be placed on other systems, which then have to compensate.

Resilience to stress

Resilience (i.e. protective factors) to stress exposure includes the psychological, physiological and behavioural dimensions. The physiological aspect of resiliency refers to the body’s ability to adapt to adverse conditions when functioning is challenged. This involves the interaction of the central, cardi-

ovascular, metabolic and immune functions (42). A well-functioning, resilient system could also be characterized by its circadian rhythm (43). Altered circadian rhythms of the stress response systems are indicators of chronic stress (42, 44, 45). Perceived control, social support and adequate coping strategies are determinants of psychological resilience to chronic stressors (46). An experimental study that provoked ischemic pain and stress demonstrated that individuals scoring high on a psychological resilience scale reported less pain and psychological stress during the painful provocation than did those who scored low on resilience (47). A recent study on patients with spinal pain found that higher levels of resilience were associated with higher levels of pain acceptance and active coping strategies (48). Thus, people who are able to cope with their pain may also maintain better functioning, for instance by keeping up a physically active lifestyle despite pain (49).

The autonomic nervous system

The ANS is a key stress regulatory system in the body, and exerts its effects on peripheral target organs via centres in the central nervous system (50), including brainstem areas (e.g. the ventrolateral medulla and periaqueductal grey), the hypothalamus, and higher brain centres (e.g., the insular and anterior cingulate cortices) involved in cognitive and emotional regulation. The ANS is involved in adaptation through a regulation of various adaptive physiological and psychological processes, including cardiovascular regulation and pain (44). At the periphery, the ANS is constituted by two anatomically separated divisions: 1) the sympathetic nervous system (SNS) and 2) the parasympathetic nervous system (PNS). The most common neurotransmitters of the ANS are epinephrine (adrenergic fibres) and acetylcholine (cholinergic fibres). In addition, sympathetic activation leads to the hormonal release of catecholamine (i.e., norepinephrine and epinephrine) in the blood through the adrenal medulla. The SNS and PNS systems have typically antagonistic tonic effects on a given tissue, and their balance is essential for homeostasis. Although these systems usually act in a reciprocal manner, they can also be co-activated or independent (51). The SNS prepares the body for physical or mental challenge – “Fight or Flight” – through a variety of physiological changes (e.g. enhanced respiration and increased heart rate, blood pressure and blood flow), which promote adaptation by increasing oxygenation and nutrition to the brain, heart and skeletal muscles. In contrast, PNS activation generally promotes recuperative and anabolic processes, with a reduction in heart rate, a lowering of blood pressure and an increase in gut motility (50). Thus, PNS predominance will occur during periods of rest, most markedly during sleep, while the SNS predominates during the day when there are increasing demands, contributing to the circadian rhythm of the ANS (45, 52). A healthy ANS response to stressors usually involves both

systems and is characterized by sympathetic activation and parasympathetic withdrawal, which is quickly recovered after cessation of the stressor.

Heart rate variability and cardiac autonomic control

Heart rate variability (HRV) has been extensively used as a simple, non-invasive marker of autonomic regulation in clinical and experimental studies. HRV is based on the fact that heart rate constantly fluctuates, and that the sympathetic and parasympathetic systems have antagonistic effects on beat-to-beat (RR) intervals. Sympathetic activity accelerates heart rate, whereas parasympathetic (vagal) activity decelerates it. Thus, autonomic cardiac modulation is reflected in variations of RR intervals (53, 54), which characterize a healthy and adaptable regulation of the ANS. The parasympathetic modulated fluctuations can be observed in respiratory frequency, i.e., respiratory sinus arrhythmia (RSA). Heart rate increases during inhalation owing to vagal inhibition, while it decelerates with expiration due to vagal stimulation. A depressed RSA has been linked to various health outcomes, such as cardiovascular diseases (55, 56). Reduced RSA has also been observed among persons reporting a higher stress level during different work conditions (57, 58). Parasympathetic cardiac modulations are relatively fast (in milliseconds), while sympathetic modulations are slower (in seconds). Consequently, different frequencies of HRV provide information about the sympathetic and parasympathetic contributions to the variability.

Various statistical methods are available for calculating indices of HRV in both the time and frequency domains (54). These are all based on the length of consecutive RR intervals (i.e. inter-beat intervals (IBI)), as obtained from the electrocardiogram (ECG). Common time domain methods are the standard deviation of all RR intervals (SDNN), the square root of the mean squared differences of successive RR intervals, and the proportion of interval differences greater than 50 ms (pNN50). SDNN is an index of overall HRV, while RMSSD and pNN50 are measures of vagal activity.

HRV can also be analysed in the frequency domain by using Fast Fourier Transform or autoregression algorithms (54). The spectral power density is usually calculated in three different frequency ranges. The high frequency (HF, 0.15-0.4Hz) power shows a peak centred at the respiratory frequency, and predominantly reflects efferent vagal influences on HRV (59). Low frequency (LF, 0.04-0.15Hz) power is modulated by the baroreflexes with a combination of both the sympathetic and parasympathetic systems (53, 60). Studies have demonstrated an increased LF power with increasing sympathetic activity (61, 62) whereby the ratio between LF and HF has been considered to reflect sympathovagal balance (63), although this concept has

been a matter of debate (64). A third component is found in the very low frequency (VLF, <0.04 Hz), and is usually extracted from long-term ECG recordings. The specific ANS contribution to VLF is not clear, although it has been suggested that it reflects both sympathetic and parasympathetic activity as well as thermoregulation and vasomotor tone (60).

The sympathetic nervous system and pain

The ANS is closely involved in nociceptive processing at both the central and peripheral levels (65, 66). Brain imaging techniques show a close anatomical and functional overlap between cortical and sub-cortical structures involved in pain processing and those controlling autonomic regulation. These include, but are not limited to, the periaqueductal grey matter and rostral ventrolateral medulla located in the brainstem, thalamus and hypothalamus, the insular, anterior cingulate and prefrontal cortices, and the amygdala (32, 67). Nociceptive afferents also directly activate neurons in the spinal cord, which projects to sympathetic neurons in the same spinal segments (65). The peripheral sympathetic system, including both neural and humoral pathways, exerts a number of actions with possible implications on motor function and musculoskeletal pain (33, 68).

There is a bi-directional relationship between autonomic activation and pain. Acute pain affects the ANS in terms of an increase in sympathetic arousal. In healthy individuals, increased sympathetic activity normally leads to an increased pain threshold and suppresses pain intensity, i.e. stress-induced analgesia, which is mainly modulated by descending pain inhibition in the spinal cord. However, this can dramatically change in conditions of chronic pain or stress (69-71). For instance, persistent sympathetic activation, e.g. induced by repeated exposure to cold stressors, can lead to hyperalgesia (72, 73).

Clinical observations of pain being spatially correlated to autonomic alterations and that blocking sympathetic efferent fibres could reduce muscle pain under certain circumstances suggest a causal role of the sympathetic nervous in the development and maintenance of localized and widespread musculoskeletal pain (74-76). In contrast, in a recent experimental study of patients with fibromyalgia or NSP, a peripheral sympathetic blockade did not affect pain development during a stressful task (77).

Stress-induced muscle activity

Different models have been proposed in attempts to explain how perceived stress and low-level physical load could produce muscle pain (78-83). Con-

siderable attention has been paid to stress-induced muscle activity in work-related MSDs (84, 85). Based on the so-called “Cinderella” hypothesis (81), it has been hypothesized that those low-threshold motor units that are active first in physical work are also activated when there are high mental demands. Thus, in conditions of perceived stress, the muscle may stay activated even after the physical work, or in the pauses, which may result in muscle fatigue and pain due to overuse of these motor units. In accordance, laboratory experiments using electromyography (EMG) indicate that mental stressors induce trapezius muscle activity, which is positively correlated to cardiovascular indicators of sympathetic activation (86, 87). At a muscular level, amplification of sympathetic activity may activate nociceptors via both direct and indirect mechanisms (30, 75). Controlled experiments have shown that sympathetic stimulation modulates muscle fibre contractility (33, 88) and impairs the sensitivity of muscle spindles involved in the transmission of proprioceptive information (82, 89). The effects of chronic pain on muscle activity include the inhibition of motor neurons, reduced motor unit discharge rate, and compensatory activation of new motor units to maintain force production (68, 90). NSP has been associated with increased muscle activation during physical or mental tasks (84, 91-94), possibly owing to increased sympathetic activation among those with pain (68, 95).

Muscle blood flow

Sympathetic activity induces vasoconstriction, which needs to be counteracted by adequate vasodilatation in order to optimize skeletal muscle blood flow (96). Any imbalance between these two actions may compromise muscle blood flow (95), leading to poor washout of metabolites and nociceptive substances (97, 98). As such changes may result in a sensitization of nociceptive afferents, excessive sympathetic outflow, due to either external stressors or chronic pain, is a potential element in the development and maintenance of musculoskeletal pain (34, 82). Clinical studies have demonstrated reduced blood flow in painful muscles among patients with trapezius myalgia during different laboratory stressors, such as static contractions (91), cold stimulation (99) and acupuncture (100). A recent study on workers with and without trapezius myalgia demonstrated reduced muscle oxygenation in the pain group during prolonged computer work (101). In agreement, studies on trapezius myalgia found increased interstitial levels of metabolites, such as lactate and pyruvate (97, 98), indicating insufficiencies in metabolism. In contrast, other studies found that trapezius myalgia was associated with a lack of recovery in muscle blood flow after low-level physical work, while no differences could be observed during these tasks (98, 102). These results may support another mechanism, as proposed by Knardahl (83), in which nociceptors are assumed to be activated mechanically by the dilatation of blood vessels. It should be noted, however, that the physical load imposed in

these two latter studies was relatively low and thus possibly did not activate the sympathetic system.

The parasympathetic nervous system

There is emerging evidence of the importance of an adequate parasympathetic function to maintain health (103). A lower parasympathetic tone is a strong predictor of mortality and cardiovascular diseases (56). Studies indicate that local inflammatory processes are modulated by parasympathetic neural activation through the release of acetylcholine, which inhibits pro-inflammatory cytokine production (104). Such anti-inflammatory effects have been demonstrated in response to electrical stimulation of the vagus nerve (105). Several pro-inflammatory substances may account for peripheral sensitization in the development of MSDs (106). Diminished parasympathetic cardiac activity has been observed among persons with chronic pain (107, 108), as in other pain syndromes (70). Although this suggests a potential pathway through which parasympathetic dysregulation contributes to the onset of muscle pain, it might also reflect a state of perceived stress among these persons. Chronic stress may result in impaired autonomic regulation of cardiovascular functions (109). Several studies using HRV as an indicator of parasympathetic (vagal) activity have found an association between perceived stress at work and reduced activity of the parasympathetic nervous system (58, 110, 111). For instance, Vrijkotte et al. (58) found that high work stress was associated with higher systolic blood pressure during work and leisure time, and lower vagal tone as measured with 24-hour HRV. Similarly, in a recent prospective study (55), the authors demonstrated that higher self-reported work stress was associated with reduced HRV, in both the low and high frequency spectral components. Thus, perceived stress is a potential mediator of autonomic imbalance in conditions of chronic pain.

Aberrant autonomic regulation in chronic muscle pain

Results from several studies provide evidence of the ANS involvement in widespread pain (e.g., fibromyalgia) (41, 112). Based on 24-hour ambulatory recordings, fibromyalgia patients have shown diminished nocturnal HRV and a blunted circadian variation (113, 114). This is in accordance with findings from controlled laboratory studies, in which elevated heart rate and reduced HRV were observed in fibromyalgia patients during supine rest (108, 115). Furthermore, cardiovascular variables reflected blunted sympathetic responses in fibromyalgia during orthostatic tests (41), mental stressors (115, 116), the cold pressor test (117, 118), and isometric exercise (119). Altogether, these results indicate aberrant (i.e. deviating) ANS regulation in

fibromyalgia patients, in terms of a basal increase in sympathetic tone and reduced parasympathetic activity, with concurrent hyporeactivity of the sympathetic system in response to stressors. Similar trends have been observed in subjects with regionalized muscle pain, e.g., whiplash associated disorder (120), low back pain (121) and NSP (107, 122). In contrast, other studies did not detect marked alterations in cardiovascular regulation among subjects with NSP (116, 123). Low HRV has been associated with higher disability from chronic neck pain (124) and low back pain (125). Pain intensity was positively associated with autonomic imbalance in widespread muscle pain (126, 127), while a study on regional pain did not show such a relationship (125). A possible explanation for these conflicting findings might be that regional NSP may represent an earlier stage in the development of widespread pain (128, 129). Thus, more severe physiological alterations would be expected in the latter condition.

The studies outlined above suggest that aberrant ANS regulation, in terms of an exaggerated sympathetic outflow and/or parasympathetic withdrawal plays a causal role in the development of both widespread and regional pain conditions. However, it could also be an epiphenomenon caused by pain and its associated features, such as low physical fitness, physical inactivity, poor sleep, or psychological stress (123, 130). As such factors are rarely taken into account more convincing evidence of the ANS involvement in chronic NSP is needed. Importantly, previous studies have mainly focused on autonomic reactions to laboratory stressors. These experiments may lack ecological validity as they extend poorly to stressors in daily life. This may also reduce the predictive value of the results. Therefore, it is preferable to assess HRV during free-living conditions, including working hours, leisure time and sleep. Combining extensive laboratory assessment with monitoring in daily life may provide important information about the ANS involvement in chronic NSP.

Physical activity and health

Physical activity can be defined as any bodily movement produced by skeletal muscles that results in a substantial increase over the resting energy expenditure (131). A vast number of studies prove that regular physical activity and exercise are beneficial for health, and prevent various chronic diseases (e.g., cardiovascular disease, diabetes, hypertension, depression and pain) (132-134), as well as improve psychological well-being (132, 135) and reduce stress (136). Increasing physical activity levels markedly reduces the risk for premature all-cause mortality (137). The physiological changes (e.g., improved autonomic balance, increased bone density and muscle fibre size, attenuated inflammation, and enhanced immune function) accompanying

physical activity depend on the type, volume, frequency, and duration as well as the intensity of the activity being performed (134).

Enhanced autonomic tone is a possible pathway by which physical activity preserves cardiovascular health (132, 138, 139). Insufficient activity levels are reflected in central alterations that increase sympathetic outflow (138, 139). Moderate levels of physical activity have been associated with increased HRV (140-142), which indicates improved autonomic regulation in favour of parasympathetic predominance in more active individuals. Others have found a negative association between physical activity and resting heart rate, but no association with HRV (143). Furthermore, the level of physical activity affects cardiovascular reactivity to psychosocial stressors (144-146).

Studies indicate that increasing physical activity is a promising strategy for treating musculoskeletal pain. Practicing sports has been associated with a reduced risk of developing neck and shoulder symptoms (147, 148). Regular strength training was found to reduce pain intensity (149-151) and increase pain thresholds (152, 153) amongst persons with NSP. A recent study on women with trapezius myalgia demonstrated increased trapezius circulation in response to a low-level physical task after a ten-week intervention using leg-bicycling (154). There is also some support for daily walking as an effective intervention for reducing muscle pain (155).

Generally, 30 minutes of moderate daily exercise or 10,000 steps per day are recommended as a minimum dose, and an additional increase in activity will likely lead to further health benefits. However, this still leaves out a substantial part of the day in which many individuals may spend most of their time inactive. Recent studies indicate that inactivity and sedentary behaviour, in their own right, have adverse effects on cardiovascular health, which are independent of physical activity (156-158). There is emerging evidence that any daily activity that interrupts inactivity could maintain, or even improve, health (134). In the occupational setting, this may especially concern those with sedentary jobs.

Physical inactivity and neck-shoulder pain

Inactive behaviour is presumed to play an important role in the maintenance of MSDs (159, 160). In chronic muscle pain, fear-avoidance beliefs (49) may lead to a reduced activity level and eventually to disuse (i.e. a decreased level of physical activity in daily life) and deconditioning (i.e. a reduction in physical fitness) (161). In addition, this could perpetuate pain and cause further reductions in mental and physical health. Consistent with this model, positive associations between fear-avoidance beliefs and disability have been

reported in studies on NSP (162, 163). It has also been suggested that some individuals may be too active and continue to be active until pain or fatigue increases, thereby forcing them to become inactive (164). Thus, activity patterns can be highly variable between individuals.

Comparisons between self-reports and the objective assessment of physical activity show a discrepancy between methods, with patients underestimating their actual physical activity levels (165). This discrepancy points out the need for objective registration of daily physical activity to provide valid and reliable data. Recent studies using objective assessment methods have revealed a lower level and/or an altered temporal pattern of physical activity in patients with low back pain compared with controls (160, 166-168). However, it is still not known whether similar changes in physical activity occur in persons with chronic pain in the neck-shoulder region, and whether these are associated with autonomic imbalance. Altogether, it seems possible that pain-related changes in daily activities affect the ANS.

Treatment using heart rate variability biofeedback

Interventions targeting the ANS may be effective in reducing pain (169, 170). HRV biofeedback is a tool for inducing acute increases in HRV through slow paced breathing (171). This is mainly achieved through baroreceptor control of blood pressure oscillations via changes in the ANS cardiac tone. It is assumed that through the practice of slow breathing, autonomic reflexes (e.g. the baroreflex) are facilitated (172). Thus, HRV biofeedback has been used to treat different disorders in which ANS imbalance has been reported, such as depression, post-traumatic stress disorder and fibromyalgia (173). Resonant frequency refers to the breathing rate (about 0.1Hz) in which HRV is maximized due to a 180° phase shift between heart rate and blood pressure oscillations, which results in resonance in the cardiovascular system (172, 174). Thus, individually adjusted HRV biofeedback may be an effective intervention for people with chronic NSP.

A hypothetical model

Based on the previous literature, see for instance (41, 82, 130, 175), a hypothetical model is proposed for the possible involvement of the ANS in the pathogenesis of NSP (Fig. 2). In brief, various external exposures, alone or in combination, induce adaptive responses in the body, e.g. with increased sympathetic and reduced parasympathetic tones. If the physiological reactions are relentless, without recovery, or if the stress response systems fail to adapt adequately to the required needs, there is a risk that musculoskeletal

pain will develop. First, local effects of excessive sympathetic activation on reduced blood flow and increased muscle activation may contribute to peripheral sensitization. Second, chronic pain (i.e., nociceptive afferent stimulation) may, in turn, activate the ANS, affecting the systemic level (e.g. increased blood pressure and reduced HRV) and locally at the region of pain (e.g. augmented muscle activity and reduced blood flow). Thus, a vicious cycle may develop which aggravates the pathological condition, including a worsening of pain and fatigue. Third, this relationship is likely modified by behavioural factors, such as daily physical inactivity, perceived stress or insufficient sleep.

Based on the current model, the following hypotheses were formulated:

- Persons with chronic NSP will show signs of ANS imbalance, as compared with healthy persons.
- Imbalance in ANS regulation will be associated with physical inactivity and perceived stress.
- Treatment aimed at improving ANS regulation will be effective in reducing symptoms of NSP.

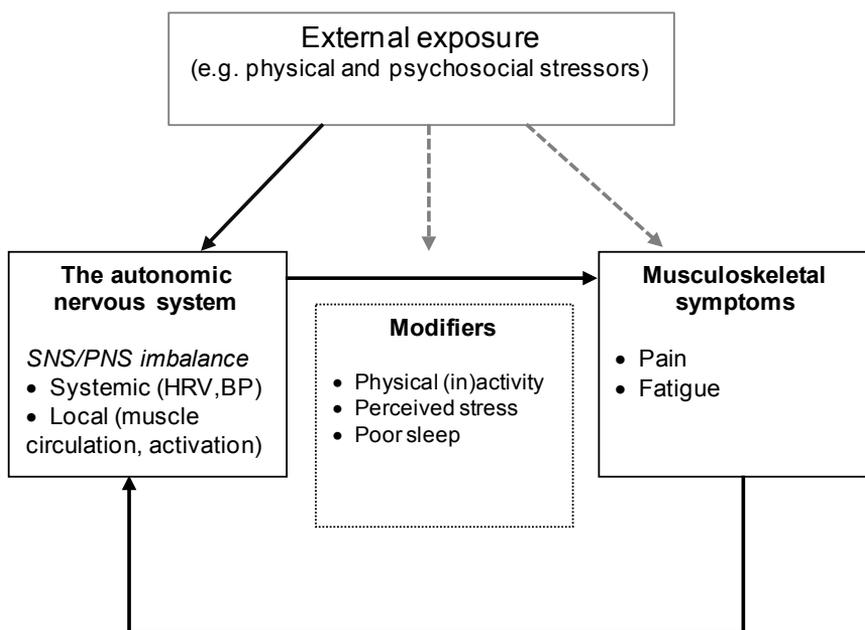


Figure 2. Hypothetical model of the autonomic nervous system involvement in the pathogenesis of chronic neck-shoulder pain. A possible causal pathway is marked with black arrows. Abbreviations: SNS = sympathetic nervous system; PNS = parasympathetic nervous system, HRV = heart rate variability; BP = blood pressure.

Overall and specific aims

The overall aim of this thesis was to investigate differences in autonomic nervous system regulation between chronic neck-shoulder pain and healthy control groups, with a focus on the influence of daily physical activity and perceived stress.

Paper I

The aim was to investigate systemic blood pressure and HRV as well as trapezius muscle blood flow and muscle activity at rest and in response to sustained hand grip, cold stimulation and paced breathing in subjects with chronic neck-shoulder pain compared with healthy controls.

Paper II

The aim was to investigate differences in autonomic regulation, physical activity and perceived stress and energy between subjects with chronic neck-shoulder pain and healthy controls by means of 24-hour ambulatory monitoring of HRV, physical activity and self-rated symptoms.

Paper III

The aim was to investigate the effects of resonance frequency HRV bio-feedback on autonomic regulation and perceived health, pain, stress and functional disability in subjects with stress-related chronic neck-shoulder pain.

Paper IV

The aim was to investigate daily physical activity, autonomic regulation and perceived symptoms (i.e., pain, stress, fatigue) during work, leisure time and sleep among workers afflicted with chronic neck-shoulder pain compared to healthy controls.

Methods

Design

All studies had a quantitative approach. Studies I, II and IV were cross-sectional. Study I was laboratory-based, while Studies II and IV focused on long-term ambulatory assessment in free-living conditions. Study III was a randomized single-blinded intervention study. The four studies were based on three data collections, including three samples of chronic NSP. Table 1 gives an overview of the data collections with their samples, study designs and methods that were included in the present thesis.

Table 1. Overview of the samples with neck-shoulder pain (NSP) and controls (CON), study designs, tests and primary outcome measures.

Data collections		Sample 1		Sample 2	Sample 3
		Study I	Study II	Study III	Study IV
Sample sizes	NSP	n = 23	n = 23	n = 24	n = 29
	CON	n = 21	n = 22		n = 27
Designs	Cross-sectional	×	×		×
	Intervention			×	
Tests	Autonomic function tests	×		×	
	Ambulatory monitoring		×		×
	Physical fitness	×			×
Objective measures	HRV	×	×	×	×
	EMG	×			
	MBF	×			
	ABP	×			
	VO _{2max}	×			×
	PA		×		×
Questionnaires	CR10	×	×	×	×
	SF-36	×		×	×
	NDI	×		×	
	SEQ		×		×

Note: In Studies I and III, the tests of autonomic function included a hand grip test, a cold pressor test and a deep breathing test.

Abbreviations: HRV = heart rate variability; EMG = electromyography (trapezius); MBF = trapezius muscle blood flow; ABP = arterial blood pressure; VO_{2max} = maximal oxygen uptake; PA = Physical activity; CR10 = Category Rating scale; SF-36 = Short Form 36-item health survey; NDI = Neck Disability Index; SEQ = Stress Energy Questionnaire.

Subjects

Characteristics of the samples with chronic NSP are shown below (Table 2).

Table 2. Characteristics of the groups with chronic neck-shoulder pain (NSP) and healthy controls (CON).

Variable	Studies I and II		Study III	Study IV	
	NSP	CON	NSP	NSP	CON
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Subjects (n)	23	22	24	29	27
Women (n)	21	20	22	13	12
Age (years)	41 (7)	41 (7)	41 (7)	41 (10)	41 (9)
CR10 (0-10)					
Current pain	2.7 (1.2)*	0.0 (0.1)	2.6 (1.2)	2.9 (1.3)*	0.1 (0.2)
Recalled pain	3.6 (1.5)*	0.1 (0.3)	3.4 (1.0)	4.2 (1.4)*	0.4 (0.8)
Pain duration (years)	9.5 (7.9)	-	5.8 (4.6)	10 (9.0)	-
NDI (0-100)	21.6 (10)	-	23.3 (11.6)	-	-
SEQ (0-5)					
Stress	2.0 (0.6)	1.8 (0.5)	-	2.8 (0.8)*	2.1 (0.6)
Energy	2.9 (0.4)*	3.2 (0.6)	-	3.5 (0.7)	3.6 (0.5)
PCS (SF-36)	43.9 (7.9)*	56.8 (1.9)	43.3 (7.7)	46.1 (6.9)*	57.2 (2.7)
MCS (SF-36)	41.6 (12.3)*	51.5 (5.7)	44.3 (12.4)	46.6 (9.7)	49.1 (8.1)

Abbreviations: CR10 = Category Rating scale; NDI = Neck Disability Index; SEQ = Stress Energy Questionnaire; PCS = physical health; MCS = mental health.

Note: - indicates data not available; *indicates a significant ($p < 0.05$) difference between NSP and CON groups (Studies I, II and IV). For PCS and MCS higher values indicate better health.

Data Collection 1 (Study I and II)

The sample from Data Collection 1 (Studies I and II) included 23 subjects (21 women) with chronic NSP and 22 healthy controls (CON), matched for age and gender. Subjects were recruited through advertising in local newspapers. Inclusion criteria for the NSP group were age between 20 and 50 years and perceived pain and/or other symptoms of muscle discomfort primarily located in the neck-shoulder region, observed for at least six months. CON had to report themselves as healthy and non-symptomatic, without current pain or previous episodes of NSP, to participate. Exclusion criteria were as follows: regular use of medications known to affect autonomic function or pain perception (e.g. antidepressant, benzodiazepine, levothyroxine, anti-inflammatory and beta-blocker drugs), diagnoses of rheumatism, diabetes, traumatic damages to the musculoskeletal system, or chronic neurological or endocrine syndromes, as well as hypertension, coronary artery diseases and substance abuse. Subjects reporting sick leave of more than two weeks during the past three months were also excluded. Subjects passing the

criteria for chronic NSP were further examined by a physiotherapist. All subjects were diagnosed with trapezius myalgia (ICD-10, code M 79.1) as they demonstrated pain, stiffness and tender points in the trapezius muscles.

Data Collection 2 (Study III)

The study included 24 subjects (22 women) aged 25 to 50 years, reporting chronic NSP and perceived stress. Subjects were recruited through a stress clinic (PBM Sweden) by advertisements on their website, recommendations from associated physiotherapists and invitations to public service employees in two cities north of Stockholm, Sweden. Respondents underwent a structured telephone interview and filled in forms to ensure that they met the case criteria for NSP, and were then randomly assigned to an intervention or control group. Inclusion criteria were: age between 20 and 50 years and perceived pain and/or other symptoms of muscle discomfort primarily located in the neck-shoulder region, observed for at least six months and persistently over the past six consecutive weeks. Exclusion criteria were similar to those of Data Collection 1, apart from that subjects could report sick leave. The inclusion- and exclusion criteria for chronic NSP were based on self-reports, which were evaluated by a psychologist.

Data Collection 3 (Study IV)

The sample from Data Collection 3 (Study IV) consisted of 29 workers (13 women) between 25 and 59 years of age, reporting chronic NSP, and 27 healthy CON (12 women) without recent history of pain. The groups were matched for age and gender, and nearly matched for type of work, i.e., office work (pain, n = 19; CON, n = 20) or production (NSP, n = 10; CON, n = 7). Subjects were recruited through advertisement at a global manufacturing company in the steel industry, at a site in Sweden, in cooperation with ergonomists and health care specialists working at the company. Inclusion and exclusion criteria (see below) were first evaluated via interviews and questionnaires, and then by a physical examination held by a physiotherapist. Inclusion in the NSP group required non-traumatic chronic pain (>6 months), localized to the neck-shoulder region (i.e., primarily the neck and/or the upper trapezius muscles). Subjects had to be between 20-59 years of age, employed, and working at least 75% of full-time. Both males and females were free to take part in the study. Exclusion criteria were the regular use of medications that could affect the ANS or pain perception, including antidepressants, benzodiazepines, beta-blockers and anti-inflammatory drugs. Further, individuals reporting co-morbidity of other disorders known to affect autonomic regulation or pain processing were also excluded, for instance diagnoses of rheumatism, diabetes, depression, chronic neurology and endocrinology syndromes or drug abuse, as well as pain of traumatic

origin. Workers reporting sick leave (more than two weeks over the past three months) were also excluded.

Ethical approval

All subjects volunteered freely and provided written informed consent. They were informed of the study aims and the details of the examinations. The studies were approved by the regional Research Ethics Committee at Uppsala University, and were carried out according to the Declaration of Helsinki.

Data collection procedures

Tests of autonomic function (Studies I and III)

In Studies I and III, three different validated tests were used to assess autonomic function (Figs. 3 and 5). The standardized examination consisted of a 15-minute resting condition followed by a sustained hand grip test (HGT), a cold pressor test (CPT) and a deep breathing test (DBT), interspaced by five-minute rests. The order of HGT and CPT was counterbalanced, and DBT was always the final test. The HGT was carried out by pressing a hand dynamometer at 30% of maximal voluntary force for three minutes. The CPT consisted of immersion of the hand up to the wrist in cold water (approximately 3° Celsius) for a maximum of three minutes. For the DBT, subjects breathed six breaths for one minute (i.e. 0.1 Hz), paced by an audio/visual stimulus.

The HGT and CPT induce sympathetic activation and parasympathetic withdrawal, mainly via mechanically and chemically sensitive receptors (HGT) or nociceptors (CPT), resulting in increased heart rate and blood pressure (176-178). The DBT induces large oscillations in RR intervals, predominantly due to parasympathetic modulation of the heart under the influence of baroreceptors (179). Parasympathetic function can be estimated by calculating the mean difference between the shortest and longest RR intervals within a breathing cycle.

During the experiment the subject was seated in a comfortable chair, individually adjusted to a semi-reclined position to provide a comfortable posture. The temperature in the room was approximately 23°C and the light was dimmed to offer a relaxing atmosphere. Prior to the recordings, the subjects were instructed to relax and breathe normally during the relaxation periods between the tests, and to avoid hyperventilation or held expiration during the static contraction and cold immersion procedures. During the measurements,

instructions were provided on the computer screen in front of the participant. Continuous physiological assessment included recordings of ECG and arterial blood pressure, as well as electromyography (EMG) and photoplethysmography (PPG) using the Biopac system (Biopac Systems inc, USA) and a specially designed PPG probe (180).

Ambulatory monitoring (Studies II and IV)

In Study II the subjects underwent 24-hour ambulatory monitoring of HRV, objective physical activity and perceived stress and energy (Fig. 3). The ambulatory registration period covered two days, including both daytime hours and sleep. The subject wore a recording device (IDEAA, MiniSun, Fresno, USA) that continuously monitored physical activity and ECG. Perceived stress and energy were rated repeatedly (i.e. morning, mid-morning, day, afternoon and evening) using a paper diary. Prior to the ambulatory assessments, anthropometric measurements, questionnaires and pain ratings were assessed, activity sensors and electrodes were attached to the subject, and the examiner gave information on equipment usage.

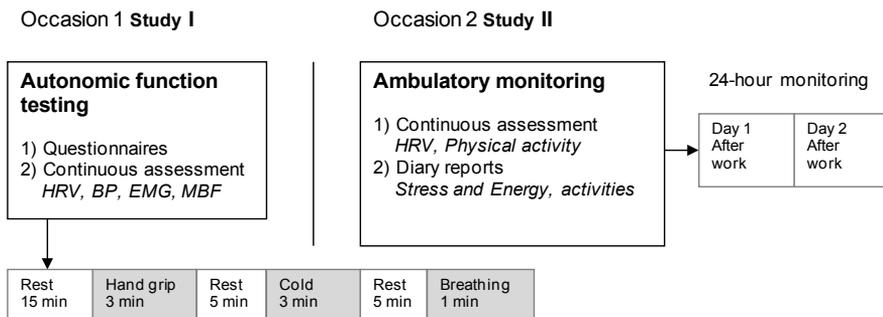


Figure 3. Protocol used in Data Collection 1 (Studies I and II). Abbreviations: HRV = heart rate variability; BP = blood pressure; EMG = electromyography; MBF = muscle blood flow.

The protocol used in Study IV is depicted in Fig. 4. The subjects underwent long-term ambulatory monitoring of physical activity (seven days), HRV and perceived pain, stress and fatigue (72 hours). The subjects wore an accelerometer for the assessment of physical activity, a heart rate monitor for the assessment of RR intervals, and an electronic diary for the assessment of momentary ratings and GPS. Questionnaires about pain, stress and energy, general health, sleep and physical activity were filled in prior to the measurements. A paper diary was used to assess work hours, leisure time and duration sleep, as well to rate daily pain, stress and energy for each day,

respectively. After completing the recording, subjects estimated their overall physical activity level during the week.

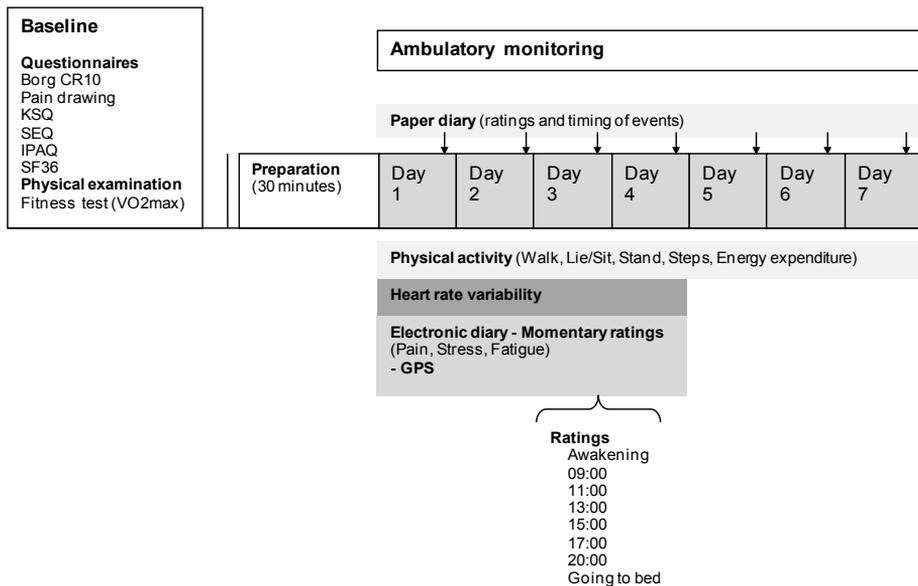


Figure 4. Protocol used in Data Collection 3 (Study IV). Abbreviations: KSQ = Karolinska Sleep Questionnaire; SEQ = Stress Energy Questionnaire; IPAQ = International Physical Activity Questionnaire; SF36 = Short Form 36-item health survey; GPS = Geographical Positioning System.

Heart rate variability biofeedback (Study III)

In Study III the intervention group received ten weekly sessions of HRV biofeedback (181), led by a psychologist. The protocol is shown in Fig. 5. Ratings of pain, disability, general health, stress, anxiety and depression were collected prior to the intervention, one week after, and six months after. In addition, HRV was assessed during rest and functional tests (see Study I) to evaluate possible effects of treatment on autonomic regulation. Controls took part in Sessions 1 and 10. During the intervention the breathing task consisted of slow paced breathing. The subjects were provided continuous HRV biofeedback by observing their changes in heart rate that occurred synchronously with each breath during the breathing phase. During Session 1 subjects were to breathe slowly, following a visual pacer, which was set alternately at different rates (6.5, 6, 5.5, 5 and 4.5 breaths per minute). The paced breathing periods (two minutes) were separated by two minutes of free, non-paced breathing. The optimal breathing rate (i.e. the resonance frequency), as defined by the breathing rate that induced the largest HRV

spectral power in the LF range, was individually detected at the first Session, and repeated at Session 10.

For Sessions 2-9, the intervention group practiced at the particular frequency detected in Session 1. Each session included four five-minute periods of resonant breathing with two minutes of rest after each period. The subjects were instructed to try to maximize their HRV as well as to attain the phase between respiration and heart rate changes as closely as possible. End tidal carbon dioxide (CO₂) was assessed to ensure that hyperventilation did not occur. Between sessions, subjects were instructed to practice paced breathing at home, for at least 15 minutes five days a week, using a pacer installed on their home computer. Controls were instructed to perform their usual activities and were not refrained from any medical or behavioural treatment, besides those stated as exclusion criteria.

Physiological signals were extensively monitored during the treatment sessions using the J&J-Engineering I-330-C-2 Physiological Monitoring System (J&J Engineering, Poulsbo, WA), including HRV, respiration rate, CO₂, oxygen saturation and temperature of the finger.

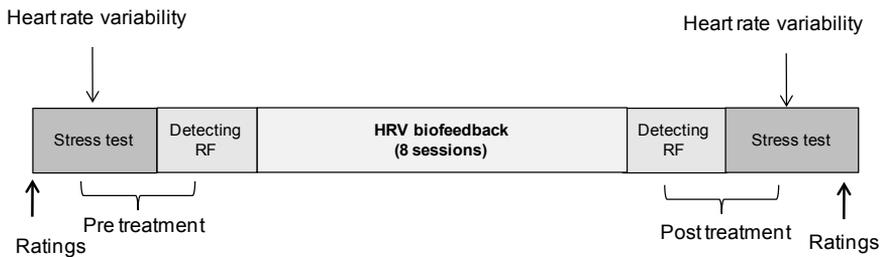


Figure 5. The treatment protocol used in Data Collection 2 (Study III). Abbreviations: RF = resonance frequency; HRV = heart rate variability.

Data processing and analysis

Objective measures

Heart rate variability (Studies I – IV)

In Studies I and III, a bipolar ECG was recorded continuously during rests and functional tests using the Biopac system (Biopac Systems Inc, USA), with 0.5-200Hz bandpass filtering, 500 times gain and 2000Hz sampling rate. Electrodes were placed on the left side of the chest and the distal end of

the sternum. A reference electrode was placed on vertebra C7. The signals were imported to Spike2 version 6.10 (Cambridge Electronic Design) for additional processing and analysis of HRV. In Study II, 24-hour ECG was recorded using the IDEEA (MiniSun, Fresno, USA) with a three lead configuration. In Study IV, 72-hour continuous RR intervals were collected using Firstbeat Bodyguard (Firstbeat Technologies Ltd, Jyväskylä, Finland), and analysed using the proprietary software (Firstbeat HEALTH, version 3.1.1.0, Firstbeat Technologies Ltd, Jyväskylä, Finland). In order to derive indices of HRV, all RR intervals from the ECG recordings were plotted against time for the visual inspection and semi-automatic editing of artefacts using linear interpolation. The artefact detection algorithm used in Study IV was in accordance with Saalasti (182).

Based on the RR interval time series, HRV were further analysed in both the time and frequency domains according to the Task Force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology (54). The time domain indices of HRV were SDNN (the standard deviation of RR intervals), pNN50 (the proportion of the number of successive differences between adjacent pairs of RR intervals greater than 50 ms) and RMSSD (the square root of the mean squared differences of successive RR intervals). In the frequency domain of HRV, spectral power density (ms^2) was calculated in the very low frequency (VLF <0.04 Hz), the low frequency (LF 0.04-0.15Hz) and the high frequency (HF 0.15-0.4Hz). Time frequency analysis of HRV was used in order to assess changes in HRV over time in Study IV (182).

To investigate the diurnal pattern of HRV in Study II, 24-hour data were extracted and averaged for the *evening* (between the hours of 18.00 and 19.00 as well as 20.00 and 21.00), *sleep* (one-hour segment with low and stable heart rate: 01.00-03.00), *morning* (the first hour with physical activity after awakening 04.00-08.00) and *day* (10.00-11.00; 13.00-14.00). In Study IV, 72-hour HRV was extracted on an hour-to-hour basis and averaged for work hours, leisure time and sleep based on diary self-reports.

Arterial blood pressure (Study I)

In Study I, arterial blood pressure was monitored using a pressure sensor (NIBP100B-R, Biopac Systems Inc, USA). The sensor was placed directly above the radial artery and semi-continuously registered arterial blood pressure, averaged over 12 pulses. Diastolic and systolic blood pressure were calculated using Acqknowledge 3.8 software.

Electromyography (study I)

In study I, superficial muscle activity was quantified based on recordings with surface EMG (Biopac Systems Inc, US). Bipolar Ag/AgCl electrodes

were placed bilaterally on the upper part of the trapezius muscles, medial to the midpoint of C7 and acromion. The signal was sampled at a sampling rate of 2000Hz, amplified 1000 times and low-pass filtered at 1000Hz. EMG was imported to Spike2 version 6.10 (Cambridge Electronic Design) for offline analysis, and the signal was further high-pass FIR filtered at 35Hz. Reference EMG root-mean-square (EMGrms) was taken during a submaximal reference contraction with bilateral arm elevation in the frontal plane, abducted to 90°. EMGrms was sampled during the middle ten seconds of the contraction, which was used for normalizing EMGrms. The noise level of the EMG signal was derived from the lowest five-second period from the complete measurement, and subtracted from all samples.

Muscle blood flow (Study I)

In Study I, photoplethysmography (PPG) was used to quantify local changes in trapezius muscle blood flow. In PPG, light is directed towards the skin and the light is absorbed and scattered in the tissue. A small amount of the light is detected by a photodetector placed, e.g., adjacent to the light emitting diode (LED), and the signal reflects both changes in blood flow and blood volume beneath the probe. A specially designed PPG probe (180) was placed bilaterally on the upper trapezius muscles, distal to the midline between C7 and acromion. In brief, the probe consisted of two photodetectors, two green (560nm) LEDs and two near-infrared (804nm) LEDs embedded in black silicon. The centre-to-centre distance between LEDs and photodetectors was 3.5 mm and 25 mm for the wavelengths 560 and 804, respectively. The amplitude of the pulsatile component of the PPG signal (PPG AC) depends on the pulsatile pressure, pulsatile blood flow, pulsatile blood volume and the number of blood vessels circulating blood in the underlying tissue. During the experiment, the peak-to-peak amplitude was calculated and averaged over 60-second segments and expressed as percentage of baseline values.

Daily physical activity (Study II and IV)

Physical activity (PA) was monitored using two different devices (II, IV). In Study II, objective registration of PA was performed using the Intelligent Device for Energy Expenditure and Activity (IDEEA, MiniSun, Fresno, USA). The IDEEA uses five sensors (i.e., inclinometers) attached with hypoallergenic adhesive tape to the trunk, thighs and feet. Calibration was performed with the subject in a seated position (183). Based on the combinations of these signals, data processing and analysis of various characteristics of PA were performed using the available software (Act view version 3.1, MiniSun, Fresno, USA). Duration of PA was quantified as the percentage of time spent walking, sitting, standing, reclining and lying down, as well as walking distance (kilometres). Intensity of PA was quantified as the speed of walking (metres/minute). Based on the intensity and type of PA, energy expenditure during locomotion was estimated and expressed in kilocalories.

PA variables were extracted from the whole 24-hour recording as well as from shorter periods to provide more detailed information on the temporal activity pattern.

In Study IV, PA was assessed over a week using the ActivPAL^{TM3} monitor (PAL Technologies Ltd, Glasgow, UK). This device consists of a small (35 mm x 53 mm x 7 mm), lightweight (16 g) sensor, which attaches to the thigh via self-adhesive. PA (walking) and postures (sitting/lying, standing) are monitored by a single tri-axial accelerometer that produces a continuous signal (20Hz sampling frequency) related to the movement and inclination of the thigh. Based on the duration and intensity of these activities, the metabolic equivalent (MET) was calculated as a measure of energy expenditure per hour ($\text{MET} \cdot \text{h}^{-1}$), i.e. *sitting* = 1.25 MET; *standing* = 1.4 MET; *stepping* >120 steps/minute = 4 MET; *cadence* more or less than 120 steps/minute = scaled linearly from standing (184). PA variables were extracted for each hour and averaged for work and leisure time (i.e. including both work days and work-free days).

Questionnaires

A battery of validated questionnaires and scales was used to assess the subjective experience of pain, stress and disability, as well as mental and physical health.

Pain (Studies I–IV)

The intensity of muscle pain was assessed using Borg's CR10 scale (185). This scale ranges from 0 "no pain" to 10 "extremely high pain" and allows subjects to rate numbers between the numerical anchors. Pain was assessed for the primary region of pain (i.e. the neck and/or shoulders), both momentarily and averaged over six months. In Study IV, a pain drawing was used to assess the localization of pain in different body regions (186).

Disability (Studies I and III)

The Neck Disability Index was used to assess the severity of symptoms and disability related to neck pain (187). This instrument consists of ten questions, each with six possible answers (0–5). The sum of the scores obtained is doubled to give a percentage score out of 100.

Physical and mental health (Studies I, III and IV)

The Short-Form 36-item health survey (SF-36) was used to assess general health and well-being (188). This questionnaire contains 8 sub-indices that address limitations in different aspects of daily life: General health, physical function, social function, physical role, emotional role, bodily pain, mental health and vitality. The scores are normalized to percentage (0-100), where-

by a higher number indicates better perceived health. In addition, these indices create two summary scales, physical health and mental health, whereby a value of 50 (SD=10) represents the normative population mean.

Stress and energy (Studies II and IV)

The Stress-Energy Questionnaire (3, 189) was used to measure perceived stress and energy during various daily activities. This validated instrument contains two scales. The stress scale includes six items ranging from positively evaluated low activation adjectives (“rested”, “relaxed” and “calm”) to negatively evaluated high activation adjectives (“tense”, “stressed” and “pressured”). The energy scale includes six items, ranging from negatively evaluated low activation adjectives (“dull”, “inefficient” and “passive”) to positively evaluated high activation adjectives (“active”, “energetic” and “focused”). The checklist uses a six-point response scale (0-5), ranging from “not at all” to “extremely”. The stress and energy dimensions are calculated by averaging the six items for each scale, after reversing items standing for low stress and energy, respectively. Thus, low-to-high values are indicative of low-to-high perceived stress and energy levels.

Statistical analyses

Study I

T-tests were used to test differences between NSP and CON groups in physiological variables at rest. Repeated measures analysis of variance (ANOVA) with *group* (two-levels) \times *time* (three-levels) were conducted to investigate differences between NSP and CON groups in response to sustained hand grip, the cold pressor test and the deep breathing test, respectively. Mann Whitney U-tests were applied to muscle blood flow due to violations of the normality assumption. Spearman correlation coefficients were carried out to explore the relationships between symptoms and cardiovascular variables.

Study II

Repeated measures ANOVA (*group* two levels \times *time* four levels) were used to investigate differences between NSP and CON groups in 24-hour HRV, physical activity and perceived stress and energy, with *group* (NSP-CON) as a between-subjects factor, and *time* of day as a within-subject factor. T-tests were applied to investigate group differences in overall physical activity. Analysis of covariance (ANCOVA) were used to adjust for the effect of physical activity (total walking time) and averaged stress ratings on HRV.

Spearman's correlation coefficients were used to explore possible relationships between physical activity and pain intensity in the NSP group.

Study III

Repeated measures ANOVA (*group* × *time*) were conducted to test the effects of HRV biofeedback treatment on self-reports (i.e., pain intensity, perceived health, disability from pain, stress-related symptoms, and anxiety and depression), as well as HRV at rest and in response to static hand grip, cold pressor test, and deep breathing, with *group* (intervention-control) as a between-subjects factor and *time* (pre-post intervention) as a within-subject factor.

Study IV

Repeated measures ANOVA were used to analyse the main effect of *group* (two levels, NSP-CON), *time* (two levels, work-leisure) and the interaction (*group* × *time*) for physical activity, i.e. energy expenditure (METs/hour), steps and duration walking, sitting/lying and standing. ANOVA (*group* × *time*) were also used for HRV and momentary ratings of pain stress and fatigue, with *group* (two levels, NSP-CON) as a between-subjects factor, and *time* (three levels, work-leisure-sleep) as a within-subject factor. In addition, ANCOVA models were used to test the influence of physical activity (total METs/day and mean METs/hour during work, leisure time, and the change from work to leisure time), sleep quality and momentary symptom ratings on HRV. The relationship between physical activity (mean METs/hour at work and leisure time) and nocturnal HRV was explored using Pearson's correlation coefficients.

In all of the studies, SPSS statistical software (IBM, US) was used to perform the statistical analyses. P-values <0.05 were considered as significant.

Main results

Autonomic reactivity to laboratory tests (Study I)

The results from the resting condition yielded a diminished resting HRV in the group with NSP (LF $p<0.05$; SDNN $p<0.05$) compared with CON. In response to static hand grip, the NSP group showed attenuated blood pressure and increased HRV (LF $p<0.05$, normalized LF $p<0.05$) as compared with CON, whereas no group difference was observed during deep breathing. Trapezius EMG and PPG indicated elevated muscle activity and blunted muscle blood flow in the NSP group during both static hand grip and cold stimulation ($p<0.05$), in comparison with CON. Only the hand grip test could discriminate between NSP and CON in trapezius muscle blood flow and EMG (Fig. 6), as well as for HRV and systemic blood pressure.

In the NSP group, moderate relationships were found between self-reported symptoms and some of the cardiovascular variables at rest. There was a positive relationship between pain intensity and blood pressure (Systolic $r = .48$, $p<0.05$; Diastolic $r = .52$, $p<0.05$) and a negative relationship between pain intensity and HRV (SDNN $r = -.44$, $p<0.05$). Neck disability correlated negatively with normalized LF ($r = -.42$, $p<0.05$).

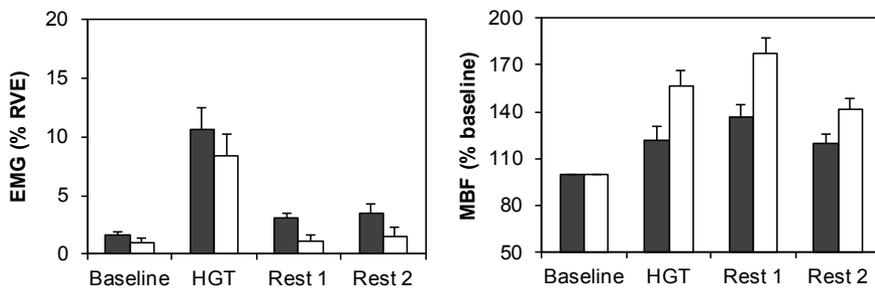


Figure 6. Study I, mean ipsilateral trapezius muscle activity (EMG) and muscle blood flow (MBF) during the hand grip test (HGT), and the first- and second-minute post test in the neck-shoulder pain group (dark bars) and the control group (white bars). Error bars represent standard errors; RVE = reference voluntary exertion.

Ambulatory heart rate variability (Studies II and IV)

In Study II, ANOVAs revealed significant main effects of group (NSP-CON) for RR intervals and all HRV indices ($p < 0.05$), which indicated a higher heart rate and lower HRV in NSP than CON. Interaction effects ($group \times time$) were found for pNN50, SDNN, VLF and LF ($p < 0.05$). This indicated a blunted circadian variation of HRV in chronic NSP as compared to CON, with diminished HRV observed during sleep (p50NN) and day (SDNN, LF, VLF) in the NSP group (Table 3). These results remained significant when adjusted for perceived stress and percentage of time walking.

Table 3. Mean (SD) of heart rate variability in neck-shoulder pain (NSP, N = 19) and control (CON, N = 18) groups.

Measure		Evening Mean (SD)	Sleep Mean (SD)	Morning Mean (SD)	Day Mean (SD)
RRI (ms)	NSP	724 (94)	890 (122)*	648 (69)*	699 (84)*
	CON	761 (101)	981 (98)	713 (75)	774 (83)
SDNN (ms)	NSP	63 (16)	56 (18)	71 (23)	59 (11)*
	CON	68 (20)	67 (16)	84 (24)	82 (21)
pNN50 (%)	NSP	6.7 (8.1)	11.0 (11.9)*	2.3 (2.0)*	5.6 (4.1)
	CON	9.2 (11.5)	22.6 (14.4)	6.7 (9.0)	10.5 (9.6)
HF (log ms ²)	NSP	5.23 (0.81)	5.61 (0.85)*	4.67 (0.63)*	5.15 (0.79)*
	CON	5.51 (0.79)	6.44 (0.75)	5.32 (0.80)	5.75 (0.68)
LF (log ms ²)	NSP	6.48 (0.61)	6.43 (0.68)*	6.48 (0.55)*	6.68 (0.50)*
	CON	6.72 (0.59)	7.05 (0.58)	6.90 (0.66)	7.05 (0.44)
LFnorm (%)	Pain	75 (9)	67 (13)	85 (5)	80 (7)
	Control	74 (7)	62 (14)	81 (9)	76 (9)
VLF (log ms ²)	Pain	7.26 (0.55)	6.99 (0.84)	7.58 (0.58)	7.33 (0.46)*
	Control	7.43 (0.56)	7.37 (0.59)	7.90 (0.66)	7.92 (0.56)

Note: *significant post hoc t-test ($p < 0.05$).

Abbreviations: RRI = RR intervals; HF = high frequency power; LF = low frequency power; VLF = very low frequency power; LFnorm = low frequency power in percentage of total power.

In Study IV, workers with chronic NSP had shortened RR intervals and lower HRV as compared with the CON group. Main effects of *group* (NSP-CON) were found in SDNN, RMSSD and VLF power ($p<0.05$). Interaction effects (*group* \times *time*) indicated a different pattern (work-leisure-sleep) of HRV in the NSP group, as expressed in shortened RR intervals and reduced HRV (RMSSD, VLF, LF: $p<0.05$; HF and LF/HF $p<0.1$) during work and sleep hours, but not in leisure time, as compared to CON (Fig. 7). When physical activity in leisure time was used as a covariate in the model, only VLF and LF spectral power reached significance. Altogether, this reflected a reduced autonomic modulation of the heart in chronic NSP, predominantly due to an attenuated parasympathetic activation during sleep.

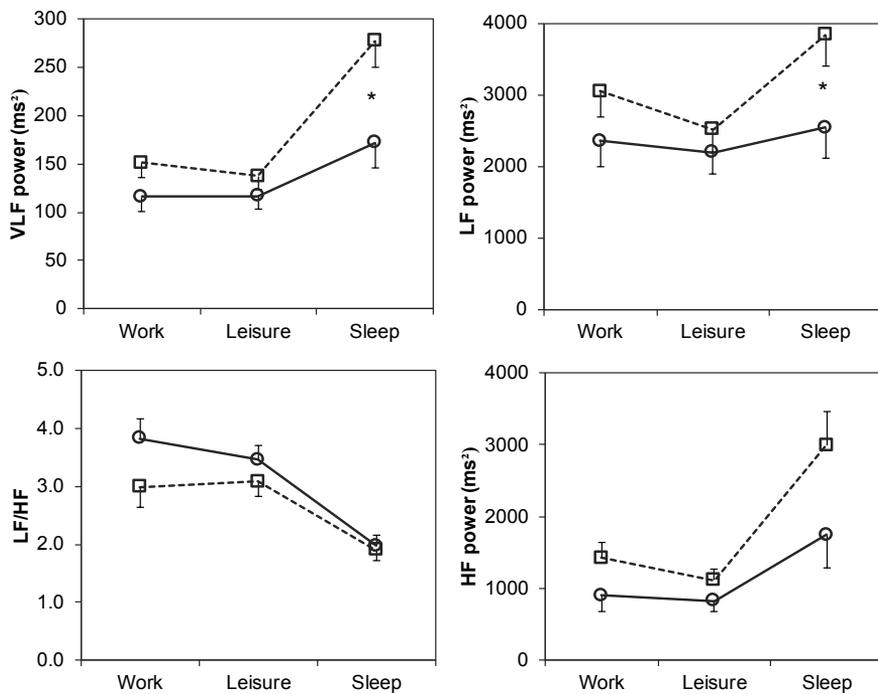


Figure 7. Study IV, mean heart rate variability spectral power in neck-shoulder pain (solid lines) and control groups (dashed lines). Error bars indicate standard errors; *denotes a significant ($p<0.05$) group difference (post hoc).

Associations between physical activity and heart rate variability (Studies II and IV)

In Study II, ANCOVAs revealed that HRV indices were affected by daily physical activity (walking time) but not by perceived stress. The circadian variation of HRV was more prominent among those persons who spent more time walking. Physical activity did not affect the group differences (NSP-CON) in HRV.

In Study IV, ANCOVAs indicated positive associations between physical activity (METs/day) and HRV. Occupational and leisure time physical activity were both positively associated with the changes in HRV (work-leisure-sleep). Correlations indicated positive relationships between physical activity in leisure time and HRV during sleep, while no such relationship was observed for physical activity during work (Table 4). Momentary ratings of pain, stress or fatigue (CR10) were not correlated to HRV.

Table 4. Correlations between nocturnal heart rate variability and physical activity (mean MET/h) at work, leisure time and the change from work to leisure time.

	MET work	MET leisure	MET change
	<i>r</i>	<i>r</i>	<i>r</i>
RRI	0.09	0.38*	0.34*
SDNN	0.10	0.33*	0.27
RMSSD	-0.03	0.32*	0.36*
VLF	0.01	0.26	0.27
LF	0.09	0.27	0.22
HF	-0.02	0.33*	0.37*
LF/HF	0.03	-0.23	-0.27

Note: *denotes a significant correlation ($p < 0.05$).

Abbreviations: RRI = RR intervals; SDNN = SD of RR intervals; RMSSD = root mean square of successive differences between RR intervals; VLF = very low frequency power; LF = low frequency power; HF = high frequency power; LF/HF = ratio between low and high frequency power.

Daily physical activity (Studies II and IV)

For overall (24-hour) physical activity (Study II) the NSP group spent more time lying down than CON ($p < 0.05$), whereas no difference between groups was found for duration sitting, standing or walking. Interaction effects ($group \times time$) indicated a different temporal activity pattern between groups: NSP spent more time lying and less time walking during the evening, and less time lying and more time walking during the morning, compared with CON ($p < 0.05$). In Study IV, workers with chronic NSP showed a

different physical activity pattern than CON, mainly with reduced physical activity (i.e., walking time, step count and METs per hour: all $p < 0.05$) during leisure time (Fig. 8).

In Study II, current pain intensity assessed prior to the ambulatory measurement correlated negatively with total walking time ($r = -.525$; $p = 0.012$) and distance ($r = -.425$; $p = 0.049$). These correlations were not significant for retrospectively recalled pain.

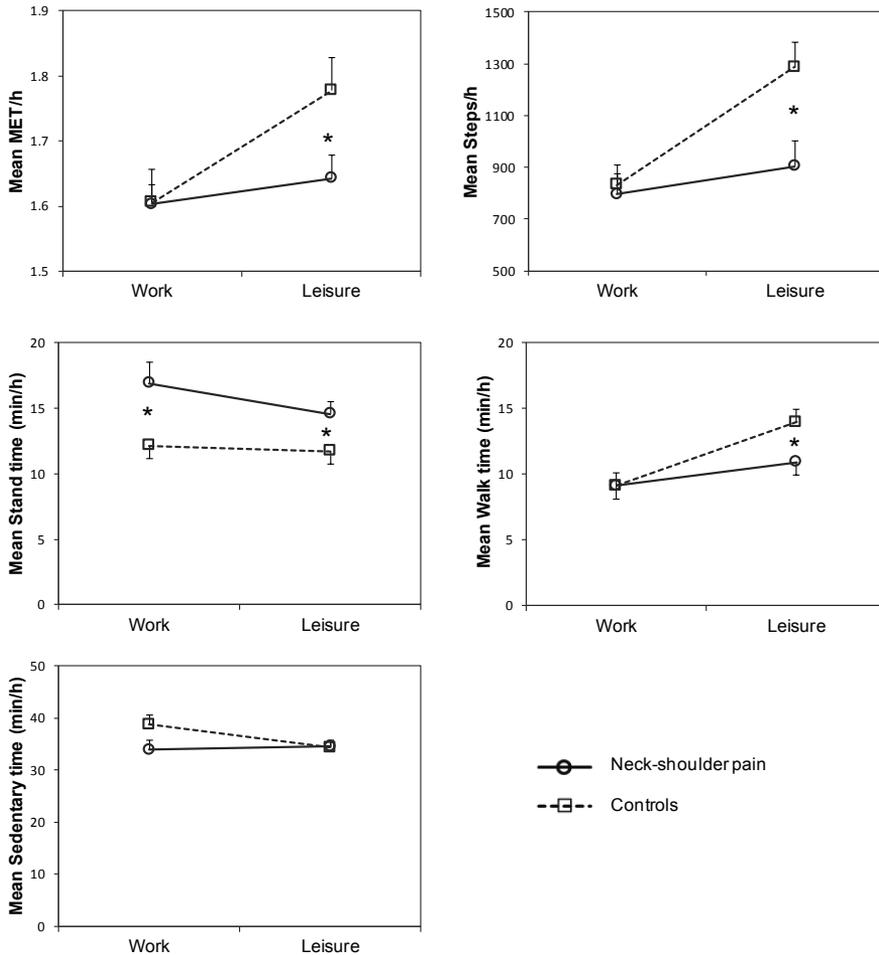


Figure 8. Mean physical activity (Study IV) during work hours and leisure time on work days in neck-shoulder pain and control groups. Bars represent standard errors. *denotes a significant ($p < 0.05$) group difference (post hoc test).

Perceived stress and energy (Studies II and IV)

In Study II there was no group difference in perceived stress level, whereas perceived energy was found to be lower in NSP than CON ($p < 0.05$). However, in Study IV workers with NSP demonstrated an increased stress perception compared to CON ($p < 0.05$). This was consistent between recalled and momentary stress ratings using the Stress-Energy Questionnaire and CR10 ratings, respectively. NSP demonstrated higher fatigue ratings during work and leisure as compared to CON ($p < 0.05$), but not during the evening prior to sleep (Study IV).

Treatment effects on self-reports and autonomic reactivity (Study III)

For the subjective reports, there were significant interactions ($group \times time$) for vitality, bodily pain and social function as measured with SF-36 ($p < 0.05$). This indicated a stronger improvement in perceived health among those who received HRV biofeedback than the control group (Fig. 9). No treatment effect was observed for pain intensity, disability or stress-related symptoms, or for anxiety and depression.

For HRV at rest, an interaction effect ($group \times time$) was found for LF ($p < 0.05$), indicating increased HRV at rest after the intervention as compared with the control group. No significant effects were observed for the other time and frequency domain measures of HRV.

For autonomic reactivity to sustained hand grip, interactions ($group \times time$) were found for RR intervals, pNN50 and LF (log) ($p \leq 0.05$) in terms of increased reactivity after the intervention in the treatment group compared to the control group. Similar interaction effects were found during the cold pressor test in RR intervals and pNN50 ($p < 0.05$). There was no interaction effect ($group \times time$) for HRV during the deep breathing test.

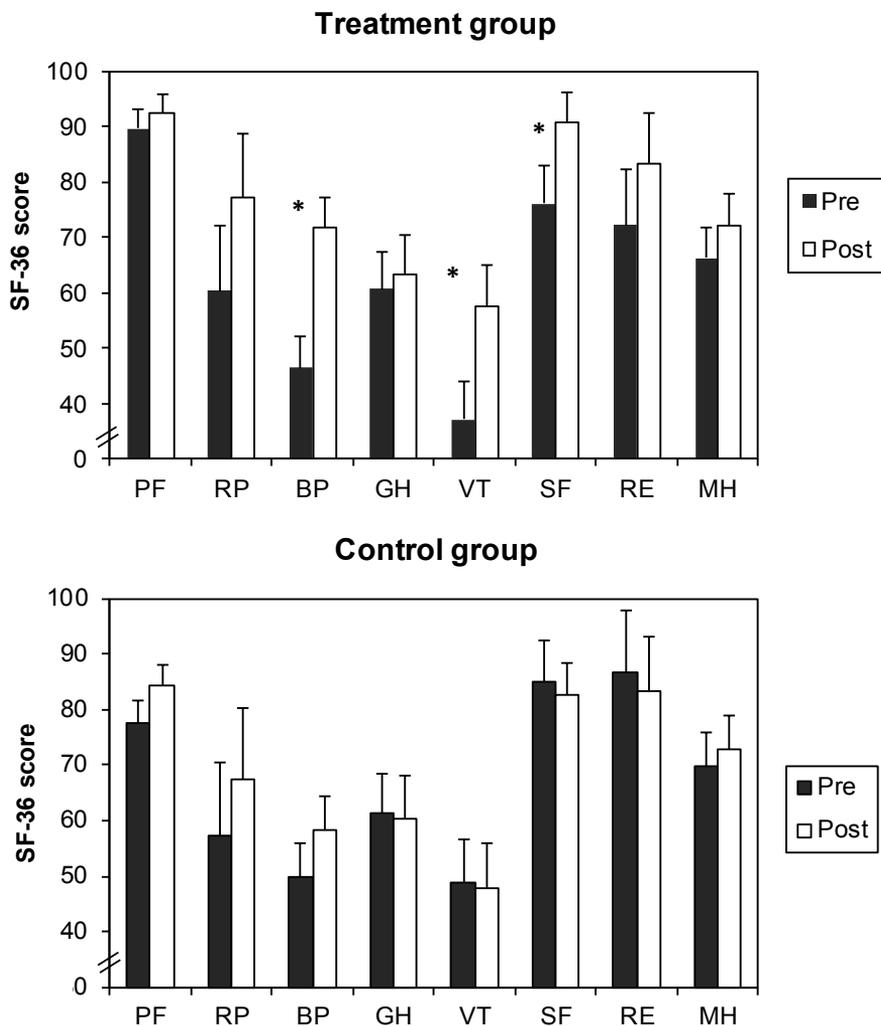


Figure 9. Mean SF-36 scores in treatment and control groups, before and after treatment. Higher scores reflect better health. Error bars represent standard errors; *indicates a significant ($p < 0.05$) interaction effect ($group \times time$). Abbreviations: PF = physical function; RP = physical role; BP = bodily pain; GH = general health; VT = vitality; SF = social function; RE = role emotional; MH = mental health.

Discussion

The overall aim of this thesis was to investigate differences in autonomic regulation between chronic neck-shoulder pain and healthy control groups, with a focus on the influence of physical activity and perceived stress. In addition, the effectiveness of resonance HRV biofeedback for treating neck-shoulder symptoms was explored. The main findings of the empirical studies are briefly summarized below.

Main findings

Studies I, II and IV demonstrated group differences in resting HRV during rest and sleep, with diminished HRV observed in the NSP group. In Study I there were signs of altered autonomic reactivity to the hand grip and cold pressor tests in the NSP group compared with CON, as reflected in HRV, blood pressure and trapezius blood flow and muscle activity. In Studies II and IV different patterns in physical activity were found between groups, with reduced leisure-time physical activity observed in chronic NSP. Associations between physical activity and HRV were demonstrated in Studies II and IV, whereas perceived stress was not associated to HRV. In Study III, positive effects of a ten-week intervention using resonance HRV-biofeedback were found on health ratings and autonomic regulation.

Autonomic regulation in chronic neck-shoulder pain

The ANS is a complex, adaptable system involved in the regulation of vital functions, mainly via activity in sympathetic and parasympathetic efferent nerves. These two branches of the ANS act in concert to preserve intrinsic homeostatic processes under various internal or external challenges. Impaired function of either component may result in insufficient adaptation to stressors and eventually to chronic disease. Different explanatory models of MSDs have paid attention to the ANS as an element of the pathogenesis of regional muscle pain, see for instance (28, 82, 190), while the evidence of ANS imbalance in chronic NSP has been inconclusive.

The results of this thesis indicate aberrations in ANS regulation among persons with chronic NSP as compared to healthy CON. Specifically, diminished HRV was found at rest (Study I) and during night time sleep (Studies II and IV). This reflected a shift in the basal autonomic state towards a reduced parasympathetic activation, and perhaps enhanced sympathetic activity, among those with pain. These results add to previous laboratory studies which demonstrated increased resting heart rate in groups with chronic NSP (107) or trapezius myalgia (123). Other studies did not find such alterations in patients with chronic NSP (116, 122), although none of those mentioned above assessed HRV, which could have revealed possible alterations not necessarily reflected in heart rate or blood pressure.

The circadian rhythm of the ANS is reflected in day/night differences in HRV (45), particularly with enhanced parasympathetic activation (e.g., increased HRV) during sleep as compared to daytime (191). The current finding of a blunted circadian rhythm of HRV in the NSP group indicates that chronic pain might enhance sympathetic predominance, which would be in line with studies on chronic widespread pain (114, 127, 192). To our knowledge, the current studies are unique in showing reduced nocturnal HRV in subjects with chronic NSP. Further, the results were rather consistent between two different samples, and between the laboratory and ambulatory conditions. Also, Studies II and IV indicate that recordings of nocturnal HRV provide an adequate window of intrinsic autonomic regulation.

It was hypothesized that subjects with NSP would show signs of altered autonomic reactivity to physical stressors. In Study I, a battery of standard tests was used. Both systemic (i.e., LF-HRV and blood pressure) and local (i.e., trapezius muscle activity and blood flow) variables indicated an altered sympathetic response to sustained contraction in chronic NSP. In agreement, blunted blood pressure responses to exercise were previously found in NSP compared to healthy subjects (107, 193). In other studies, psychosocial stressors with low physical loads did not induce marked cardiovascular alterations in persons with NSP (116) or among patients with trapezius myalgia (123). Previous studies have shown impaired microcirculation in painful trapezius muscles during static contractions (91, 194), while normal trapezius blood flow has been reported in NSP during low intensity work (102). This would indicate that persons afflicted with chronic NSP are intolerant to fatiguing exercise. General fatigue is also more common in NSP than among healthy subjects (12). It was argued that such symptoms could develop secondary to ANS imbalance (41).

During the cold pressor test, which induced intense pain, group differences were found in terms of enhanced muscle activation (ipsilateral trapezius) and reduced blood flow (contralateral trapezius) among those with chronic NSP,

as compared to CON. In concert, a previous study on trapezius myalgia demonstrated impaired local circulation during cold stimulation, while systemic cardiovascular measures were unaltered (99). Experiments indicate that sympathetic activation affects muscle contractility (88, 195) and induces vasoconstriction (96). The exact mechanism responsible for impaired muscle blood flow in NSP could not be established here. Either sympathetic hypo- or hyper-reactivity could have occurred in the pain group. Still, the results from Study I imply an aberrant sympathetic regulation at the muscular level in chronic NSP.

Interestingly, during the cold pressor test, NSP reported higher pain intensity than CON, which was positively correlated to enhanced muscle activation in the pain group. This might suggest that central mechanisms were involved. However, as assessment of pain thresholds was not carried out we will not speculate further about central sensitization.

Physical activity patterns in chronic neck-shoulder pain

Physical activity was assessed objectively in two samples with NSP. In both studies (II and IV), group differences were found with respect to the pattern of activity over the day. The NSP group demonstrated lower activity levels in the evening and more activity in the morning, as compared to CON. In Study IV workers with chronic NSP showed a lesser increase in physical activity from work to leisure time, in comparison with the CON group. In agreement, altered temporal patterns of active behaviour were previously observed in patients with low back pain (166, 168). A possible interpretation of this would be that chronic pain is associated with a sense of fatigue (12); thus, subjects in the NSP group may have used their resources while accomplishing activities at work, which may have led to increasing fatigue, resulting in reduced activity levels in leisure time (168). In concert, the NSP group rated higher level of perceived fatigue than the CON group did. In addition, negative correlations were found between pain intensity and total walking time and distance (Study II), which suggests lower activity levels with a higher pain intensity.

There were no marked differences in overall physical activity, although in Study II the NSP group was found to spend more time lying down. However, this could not be replicated in Study IV. Altogether, the current results may have implications on the prevention and treatment of MSDs, suggesting the need for interventions targeting the patterning of physical activity among workers with chronic NSP.

Perceived stress

Psychosocial factors are important risk-factors for work-related MSDs, as they induce perceived stress (196). Higher perceived stress was found in NSP compared with CON (Study IV), which may indicate a higher stress exposure in the pain group. Perceived stress was expected to influence on HRV. A recent meta-analysis could not confirm that chronic psychosocial factors affected autonomic reactivity to or recovery from mental stressors (197), while other studies indicated that perceived stress at work was related to reduced HRV at rest (55, 58). It seems possible that perceived stress may affect intrinsic autonomic regulation without affecting stress-reactivity. Still, in two different samples of NSP (Studies II and IV), perceived stress could not significantly explain group differences in nocturnal HRV or the within-subject variance in terms of temporal changes in HRV.

Physical activity and autonomic regulation

The body responds to different patterns of physical activity in unique ways (156). It was expected that physical activity would be positively associated with HRV. In accordance, the diurnal pattern of HRV was influenced by total physical activity (Study II) and the change in physical activity from work to leisure time (Study IV), whereby the latter relationship indicated a larger circadian variation of parasympathetic activation with higher physical activity levels in leisure time. Greater HRV at rest was previously observed among moderately active persons than in those who were less active (140). Total physical activity did not account for the attenuation of HRV in NSP, as compared to CON. However, when adjusting for the change in energy expenditure (METs) from work to leisure time, the parasympathetic HRV indices were no longer significant between groups (Study IV). This would imply that the parasympathetic attenuation in chronic NSP was modulated by low physical activity in leisure time, although it is likely that the presence of pain was the dominating factor.

In Study IV it was also found that physical activity in leisure time, but not at work, was positively correlated to HRV during sleep. This may have reflected a long-term effect of physical activity on nocturnal autonomic regulation, although the opposite direction of this relationship could not be excluded. The lack of correlations between occupational physical activity and nocturnal HRV suggests different health benefits of occupational and leisure time physical activity.

Potential confounders

The results of the current studies may have been confounded by different factors, which may have accounted for the observed group differences. Namely, the maximal voluntary force was lower in the NSP group than in the CON group (Study I). Thus, the subjects in the NSP group may have worked at lower relative contraction intensities during the hand grip test. Attenuated blood pressure might also have accounted for the blunted blood flow response in the NSP group. These factors were, therefore, adjusted for in the statistical models, and did not affect the results.

Another potential confounder was the impaired mental health component in NSP (studies I and II). However, as diagnoses previously related to ANS imbalance (e.g. depression or chronic fatigue syndrome) were excluded from the study it is unlikely that such factors affected the results.

There is a bi-directional relationship between sleep and ANS regulation (198). Poor sleep in NSP might, therefore, have been a potential confounder for the reduced nocturnal HRV in the present studies. Underlying sleep disorders may also have accounted for the increased levels of perceived fatigue observed in the NSP group compared with CON. Although there were no group differences in self-reported sleep duration in Studies II and IV, self-reported sleep quality was found to be marginally lower in NSP than CON (Study IV).

Autonomic reactions have been studied to a larger extent in widespread pain conditions, e.g. fibromyalgia (41). Patients with fibromyalgia show increased sympathetic and reduced parasympathetic tones at rest, with concurrent hyporeactivity of the sympathetic response to stressors (108, 119, 199, 200). Based on self-reports and a physical examination, it is not likely that widespread pain confounded the results.

Heart rate variability biofeedback

Given that reduced HRV has been observed in persons with chronic pain, it was hypothesized that an intervention aimed at reinstating ANS regulation by increasing HRV would be efficient in improving symptoms in chronic NSP. Thus, in Study III, HRV biofeedback was used over ten weekly sessions according to a standardized protocol (181). Although self-ratings generally improved with time, only three of the SF-36 indices (i.e. bodily pain, social function and vitality) showed significant effects related to treatment. These marginal findings might reflect the limited statistical power in the

study or causal effects due to the enhanced ANS regulation during paced breathing.

Previous studies have usually evaluated changes in HRV derived from the treatment sessions (173). In the current study, however, an extensive test battery for the assessment of ANS function was used before and after the intervention. The intervention group showed stronger improvement over ten weeks in LF-HRV at rest, and increased autonomic reactivity to hand grip and cold pressor tests, compared to the control group. This implies a beneficial effect of HRV biofeedback on autonomic regulation. However, it is also possible that the attention given to the intervention group played a role. As no treatment effect was observed for HRV during the deep breathing test, higher resting HRV after treatment might have reflected a non-specific central effect on the ANS.

Possible causal relationships

In this thesis, the causal relationships could not be established due to the cross-sectional design of three of the studies. Although speculative, the current results may be interpreted in view of previous explanatory models of MSDs. It has been suggested that the ANS plays different roles in different phases of the pathogenesis of MSDs (28, 41, 82). Initially, a hyperactive sympathetic system, e.g. due to persistent physical and/or psychosocial stressors at work, may contribute to pain via changes in muscle contractility and/or impaired muscle circulation. In chronic pain conditions, enhanced nociception may further activate the sympathetic system and inhibit the parasympathetic system, resulting in an aggravating vicious cycle. Relentless sympathetic activation may result in down regulation of adrenoceptors leading to a hypo-reactive responsiveness to stressors, e.g., physical or mental loads, contributing to tiredness and fatigue. Thus, ANS imbalance may act as a causal factor, but could also be a consequence of chronic pain. The current thesis provides preliminary support for this model by demonstrating an imbalance in ANS regulation among persons with chronic NSP.

Similar changes in the ANS may occur due to prolonged psychological stress or physical inactivity, both of which have been associated with chronic MSDs. Although there was weak support for an association between HRV and perceived stress, it cannot be ruled out that perceived stress was an initiating factor. In line with the hypothesis, lower physical activity in leisure time was partly accountable for the reduced parasympathetic activation during sleep in the pain group.

Finally, the proposed model hypothesized that treatment aimed at restoring ANS balance would improve symptoms in subjects with chronic NSP, which was partly supported in Study III.

Methodological considerations

Strength of the current studies is the use of long-term ambulatory monitoring combined with laboratory testing for the assessment of ANS regulation. The objective assessment of physical activity provided detailed and precise information on daily physical activity in subjects with chronic NSP.

Altogether, the NSP groups were characterized by chronic pain in the neck-shoulder region, poor physical health and reduced perceived energy as compared to CON (Studies I, II and IV). The groups were matched with regard to age and gender, and there were no differences in body mass index or physical fitness. None of the subjects reported sick leave, co-morbidity of chronic diseases or the use of medications affecting the ANS. Thus, it was ruled out that these factors confounded the current results.

A potential limitation concerns the generalizability of the study results. Since the sample from Data collection 1 (Studies I-II) was recruited through advertisement in newspapers it is possible that mainly persons with mild symptoms were interested in participation, in comparison with patients with more severe symptoms. Therefore, the results may not generalize to the whole population. Furthermore, the samples from Data Collections 1 and 2 were rather heterogeneous as they included a variety of occupations. In order to ensure a more homogenous sample in Study IV, both NSP and CON groups were recruited from the same company.

In Study III, it is possible that low symptom scores prior to the intervention (i.e., floor effect) prevented any further improvements in the treatment group, as compared with the control group.

Another limitation concerns the gender distribution, as there was a predominance of female participants in the current studies (I-III). Thus, the results obtained from these studies may not extend to men. Still, this could also have reflected a greater prevalence of MSDs among women than men (1). As the current thesis did not encompass the gender factor, further studies addressing this issue are needed.

Due to the cross-sectional designs of Studies I, II and IV, the causal relationships between pain, ANS regulation and physical activity could not be addressed sufficiently.

Further limitation regards the lack of pain ratings during the ambulatory measurement (Study II).

Sample sizes were relatively small, increasing the probability of false negative findings. However, power calculations were performed a priori and indicated that sample sizes were adequate for detecting clinically relevant group differences in HRV and physical activity. Considering the number of correlations performed in Study I, the association between pain intensity and HRV at rest should be interpreted with caution. Due to the limited sample size in the intervention ($n = 24$), it was regarded as a pilot study.

The studies focused on non-invasive assessment methods to avoid obtrusiveness, although other markers, in addition to HRV, could have been used to assess sympathetic function. Finally, as we did not assess the activity of the HPA axis, the possible involvement of this stress system could not be investigated.

Conclusions

In conclusion, the results of the four studies supported the hypothesis regarding the ANS involvement in chronic NSP. Systemic and local cardiovascular variables indicated autonomic imbalance among persons with chronic NSP, in terms of diminished parasympathetic activation during sleep and an altered sympathetic response to stressors. The NSP groups showed a different pattern of daily physical activity than the healthy controls did, as characterized by reduced physical activity in leisure time. Differences in physical activity were associated with ANS imbalance. Non-invasive treatment targeting the reinstatement of ANS regulation enhanced both subjective and objective indicators of health in subjects with chronic NSP.

Further studies

Further studies need to be conducted to examine the involvement of the ANS in the pathogenesis of chronic NSP. It is important to prospectively follow the time course of symptoms as well as changes in ANS regulation and physical activity to provide information about the chain of causality. Physical activity-dependent alterations in the ANS should also be investigated with respect to different exposures at work. Finally, interventions are warranted that investigate the effect of increasing daily physical activity on ANS regulation and muscle pain in persons with chronic NSP.

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Sammanfattning på Svenska

Smärta och obehag i nacke-skuldra regionen är vanligt förekommande muskuloskeletal besvär som orsakar stora kostnader för samhället såväl som lidande för den drabbade individen. Otillräcklig förståelse för de underliggande sjukdomsmekanismerna resulterar i bristfällig prevention och behandling. Forskning pekar på en obalanserad reglering i det autonoma nervsystemet (ANS) som ett möjligt element vid uppkomst och försämring av muskelsmärta. Det övergripande syftet med föreliggande avhandling var att undersöka skillnader i ANS reglering mellan personer med långvarig smärta i nacke-skuldra (NSP) och besvärsfria kontrollpersoner (CON), i relation till daglig fysisk aktivitet och upplevd stress.

Avhandlingen bestod av fyra delstudier som baserades på data från tre grupper av NSP. Skillnader mellan grupper med NSP och CON i autonom respons till standardiserade tester (statiskt handgrepp, isvatten och djupandning) undersöktes i studie I. Hjärtfrekvensvariabilitet (HRV) och arteriellt blodtryck, samt muskelaktivitet och blodflöde i trapeziusmusklerna mättes kontinuerligt under experimentet. Två fältstudier (studie II och IV) fokuserade på gruppskillnader i fysisk aktivitet, HRV och självskattade symptom under arbete, fritid och sömn. Effekten av tio veckors behandling med djupandning och HRV-biofeedback, med syftet att återhämta ANS reglering hos personer med NSP, utvärderades på upplevd hälsa, symptom och HRV (under vila och i respons till stress) i studie III.

Huvudresultaten från de fyra studierna indikerade avvikelser i ANS reglering hos personer med NSP jämfört med CON. Detta karaktäriserades av minskad parasympatisk aktivitet under vila och sömn och en förändrad sympatisk respons till stress. Gruppskillnader i mönstret av fysisk aktivitet över dagen visades i lägre aktivitet på fritiden hos NSP jämfört med CON. Daglig fysisk aktivitet var positivt associerat med HRV. Inget samband kunde visas mellan upplevd stress och HRV. Positiva effekter av intervention med HRV-biofeedback indikerades i förbättrad självrapporterad hälsa och ökad HRV jämfört med gruppen utan behandling.

Sammanfattningsvis indikerade studierna en obalanserad autonom reglering hos personer med långvarig smärta i nacke-skuldra, både på systemisk nivå (blodtryck och HRV) och lokalt i smärtsamma muskler (muskelaktivitet och blodflöde). Avvikelser i ANS reglering hos gruppen med NSP förklarades delvis av minskad fysisk aktivitet på fritiden. Prevention och behandling riktad mot återhämtning av ANS reglering kan gynna personer med NSP.

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